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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,474	04/22/2004	Brian D. Mariani	43956-121	6416

7590 04/25/2006

MCDERMOTT, WILL & EMERY
600 13th Street, N.W.
Washington, DC 20005-3096

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/829,474	MARIANI, BRIAN D.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *7,14-20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-13 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 4/22/04 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Annotated Fig 1 of US Patent 6818397.

DETAILED ACTION

Election/Restrictions

1. Claims 7, 14-20 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/8/2006. In a telephone interview with Thomas Haag on 2/27/2006, the species of SEQ ID NO: 4 was elected with traverse. Claims 7 and 22, drawn to non elected species, are also withdrawn from consideration.

2. The substitute specification, filed to fulfill the requirement of 37 CFR 1.52(b) regarding correct line spacing, submitted 7/6/2004 has been entered.

Claim Objections

3. Claims 2, 5, and 11 are objected to because of the following informalities: The claims recite "hybridize the complement", the claims should recite "hybridize to the complement". Claim 21 recites the term "wherein" twice in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 4, and 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite the following language: "an isolated oligonucleotide of the sequence of SEQ ID NO:...". It is unclear if the claim is intended to be limited to a molecule "consisting" of the indicated SEQ ID NO:, or to fragments from within the indicated SEQ ID NO:. the metes and bounds of the claim are unclear.

Claims 3, 6, 8-13 and 21 are indefinite in the recitation of "about 1" and "about 3" nucleotides. While it is clear that 1-3 nucleotides are encompassed, the term "about" when referring to a nucleotide is unclear because the term cannot encompass a portion of a nucleotide. Therefor, it is unclear if "0" nucleotides or "4" nucleotides are encompassed by the term.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-2 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Pasloske (US Pregrant Publication 20030170617, Published September 11, 2003).

Pasloske teaches a primer sequence (SEQ ID NO: 2 of Pasloske) which is identical to instant SEQ ID NO: 1.

8. Claims 2 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Verstrepen (Verstrepen et al; J. Clin. Microbiol, vol. 39, pages 4093-4096; 2001).

Verstrepen teaches a forward primer for an RT-PCR assay of enterovirus (see table 1). It aligns with instant SEQ ID NO: 1 as follows:

```
Qy          1 CCCCCTGAATGCGGCTAATC 19  (SEQ 1 of instant app)
              ||||||||||||||||||||
Db           1 CCCCTGAATGCGGCTAATCC 19 (forward primer of Verstrepen)
```

The sequence of Verstrepen has 1 nucleotide removed from the 5' end of SEQ ID NO: 1 and 1 nucleotide added to the 3' end of SEQ ID NO: 1. The extra nucleotide on the 3' end is a nucleotide from the next position on the enteroviral genome and would be capable of amplifying reverse transcribed enteroviral RNA, accordingly, the sequence of Verstrepen anticipates the sequence of claim 3. With regard to claim 2 the forward primer of Verstrepen would be capable of hybridizing to the complement of SEQ ID NO: 1.

9. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Renaud et al (WO 02/02811, Jan. 2002) as evidenced by Lee (Lee et al; US Patent 6,818,397).

Renaud teaches 2 sequences, SEQ ID NO: 70 and SEQ ID NO: 74 which would hybridize to the complement of instant SEQ ID NO: 1 and would be capable of amplifying reverse transcribed enteroviral RNA when used in conjunction with instant SEQ ID NO: 2. Positions 7-25 of SEQ ID NO: 70 are identical to instant SEQ ID NO: 1. Positions 11-29 of SEQ

ID NO: 74 are identical to instant SEQ ID NO: 1. Also, SEQ ID NO: 70 of Renaud is completely identical to positions 450-479 of the enterovirus type71 5' untranslated region and SEQ ID NO: 74 of Renaud is identical to positions 446-475 of the enterovirus type 71 5' untranslated region (see Figure 1 and SEQ ID NO: 16 of US Patent 6,818,397), and therefore either would be capable of amplifying reverse transcribed enteroviral RNA in conjunction with instant SEQ ID NO: 2.

10. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession number U55869 (1996).

The complement of Accession number U55869 is considered an inherent disclosure of the sequence of U55869. Accession number U55869 teaches a sequence of 103 base pairs, the complement of which is identical to SEQ ID NO: 2. Therefore, the complement of the accession number would be capable of hybridizing to the complement of SEQ ID NO: 2. The accession number is a sequence of the 5' NTR of an enterovirus species and thus would be capable of amplifying reverse transcribed enteroviral RNA in conjunction with instant SEQ ID NO: 1.

11. Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession number U55870 (1996).

With regard to claim 21,The specification does not define the term "having", therefore it has been broadly interpreted as "comprising", that is the claim encompasses nucleotides on either side of SEQ ID NO: 4. It is further noted that the complement of Accession number U55870 is considered an inherent disclosure of the sequence of U55870. The sequence of the complement

of U55870 comprises the sequence of SEQ ID NO: 4 (positions 17-41 are the reverse complement of SEQ ID NO: 4).

12. Claims 1, 2, 4, 5, 8-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor (Fodor et al; US Pregrant Publication 2001/0053519).

The recitation of "an oligonucleotide of SEQ ID NO:..." has been interpreted to encompass fragments from within the indicated SEQ ID NO:. Fodor teaches an array of every possible 10 mer nucleic acid molecule. The claims encompass a genus of possible sequences, such as fragments of SEQ ID NO: 1 and/or 2, as well as sequences which would hybridize to the specified sequences under stringent conditions. The disclosure of Fodor therefore anticipates the claims. With regard to claims 8-11, as the claims do not disclose any structural attributes that would distinguish a "kit" from a composition, the claims have been broadly interpreted to encompass a composition comprising the indicated sequences, which is taught by Fodor.

13. Claims 2, 5, 6, 11, 13 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee (Lee et al, US Patent 6,818,397).

Lee teaches a method of detecting enteroviruses by using primers and probes to the enteroviral 5' untranslated region (see Figure 1, SEQ ID NOS 1-15 of Lee). Lee specifically teaches regions to target on the enteroviral genome which overlap with instantly claimed SEQ ID NO: 1, 2, and 4 (see Figure 1 and annotated Figure 1 provided with this office action).

With regard to claim 2, Lee teaches the sequence of SEQ ID NO: 9, which is identical to instant SEQ ID NO: 1 from positions 9-27. This sequence would hybridize to the complement of

SEQ ID NO: 1 under stringent conditions and would be capable of amplifying reverse transcribed enteroviral RNA.

With regard to claims 5 and 6, Lee teaches SEQ ID NO: 11 which is 28 nucleotides long. Instant SEQ ID NO: 2 is the reverse complement of SEQ ID NO: 11 from positions 5-24 (the term "about 3" has been broadly interpreted to include 4 additional nucleotides on either side of instantly claimed SEQ ID NO: 2). It is noted that SEQ ID NO: 11 of Lee is degenerate at various positions, and degenerate at position 22 of the sequence of Lee (the position corresponding to position 3 of instant SEQ ID NO: 2). Lee teaches that position 22 of SEQ ID NO: 11 can be either a C, T, or A. The reverse complement of SEQ ID NO: 11 is considered inherent in the disclosure of Lee. Therefore Lee anticipates claim 5 as the reverse complement of SEQ ID NO: 11 of Lee, (which is inherently taught to have a G, A, or T at position 22) would hybridize to the complement of SEQ ID NO: 2 under stringent conditions and would be capable of amplifying reverse transcribed enteroviral RNA. Lee anticipates claim 6 as the reverse complement of SEQ ID NO: 11 of Lee (which is inherently taught to have a G, A, or T at position 22) has "about 3" (that is, 4) nucleotides added on the 5' and 3' end of SEQ ID NO: 2.

With regard to claims 11 and 13, Lee teaches to package primers and probes in kit format (see col. 10, lines 42-56) with appropriate buffers and enzymes for PCR.

With regard to claim 21, Lee teaches SEQ ID NO: 10 which is 33 nucleotides long. The reverse complement of SEQ ID NO: 10 (which is considered inherent in the disclosure of Lee) at positons 3-27 is identical to instantly claimed SEQ ID NO: 4 is therefore "comprises" (having is broadly interpreted as "comprises") instantly claimed SEQ ID NO: 4.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 3, 4, 8-13 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee and Verstrepen in view of Hogan (Hogan US Pat. 5,541,308, July 30, 1996) and Buck (Buck et al; Biotechniques (1999) 27(3):528-536).

Lee teaches a method of detecting enteroviruses by using primers and probes to the enteroviral 5' untranslated region (see Figure 1, SEQ ID NOS 1-15 of Lee). Lee specifically teaches regions to target on the enteroviral genome which overlap with instantly claimed SEQ ID NO: 1, 2, and 4 (see Figure 1 and annotated Figure 1 provided with this office action).

With regard to oligonucleotides for detecting enterovirus, Lee teaches the following structures:

a) with regard to instantly claimed SEQ IDNO: 1: Lee teaches the sequence of SEQ ID NO: 9, which is identical to instant SEQ ID NO: 1 from positions 9-27 ("p1" region in Figure 1 of Lee).

```
Qy          1 CCCCTGAATGCGGCTAATC 19  (SEQ 1 of instant app)
              ||||||||||||||||||||
Db          9 CCCCTGAATGCGGCTAATC 27  (SEQ 9 of '397 patent)
```

b) with regard to instant SEQ ID NO: 2, Lee teaches SEQ ID NO: 11 (corresponds to"p3" region in Figure 1 of Lee) which is 28 nucleotides long and includes degenerate positions. (Instant SEQ ID NO: 2 is the reverse complement of SEQ ID NO: 11 from positions 5-24 It is

noted that SEQ ID NO: 11 of Lee is degenerate at various positions, and degenerate at position 22 (the position corresponding to position 3 of instant SEQ ID NO: 2) Lee teaches that position 22 of SEQ ID NO: 11 can be either a C, T, or A (the complementary nucleotide would be G, A or T respectively).

```
Qy          1 AAGGAAACACGGACACCCAA 20  (SEQ 2 of instant app)
              ||||||||||||||||||||
Db         24 AADGAAACACGGACACCCAA 5   (reverse complement of SEQ 11 of '397
patent, note for degenerate positions "D" is the complement of "H")
```

c) with regard to SEQ ID NO: 4, Lee teaches SEQ ID NO: 10 which is 33 nucleotides long ("p2" region in Figure 1 of Lee), which is identical at positions 3-27 to the complement of instant SEQ ID NO: 4.

```
Qy          1 TCCGCTGCAGAGTTGCCCGTTACGA 25  (SEQ 4 of instant app)
              |||||||||||||||||||||||||
Db         27 TCCGCYRCRGASTTGCSCGTTACGA 3   (SEQ ID NO: 10 of '397 patent,
note for degenerate positions, "S" is the complement of "S", "R" is the
complement of "Y")
```

Lee teaches to package primers and probes in kit format (see col. 10, lines 42-56) with appropriate buffers and enzymes for PCR. Lee does not teach sequences consisting of SEQ ID NO: 1, 2, or 4, nor sequences of SEQ ID NO: 1 or 4 where 1 to 3 nucleotides are added or removed from the 5' and/or 3' end.

Verstrepen teaches an assay for detecting enterovirus in a sample using real time PCR. With regard to instant SEQ ID NO: 1, Verstrepen teaches a forward primer for an RT-PCR assay of enterovirus (see table 1). It aligns with instant SEQ ID NO: 1 as follows:

```
Qy          1 CCCCCTGAATGCGGCTAATC 19  (SEQ 1 of instant app)
              ||||||||||||||||||||
Db          1 CCCCTGAATGCGGCTAATCC 19 (forward primer of Verstrepen)
```

The sequence of Verstrepen has 1 nucleotide removed from the 5' end of SEQ ID NO: 1 and 1 nucleotide added to the 3' end of SEQ ID NO: 1. The extra nucleotide on the 5' end of instant SEQ ID NO: 1 is a nucleotide from the next position on the enteroviral genome (See Fig 1 of Lee patent).

With regard to instant SEQ ID NO: 2, Verstrepen teaches a probe for use in the assay which overlaps region "p2" and "p3" taught by Lee. Verstrepen does not teach sequences consisting of SEQ ID NO: 1, 2, or 4, nor sequences of SEQ ID NO: 2 or 4 where 1 to 3 nucleotides are added or removed from the 5' and/or 3' end.

However, Hogan teaches construction of primers for use in amplification (col. 6-7, lines 50-67, lines 1-12), and furthermore provides specific guidance for the selection of detection oligonucleotides,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (col. 10, lines 13-15). Further, Buck expressly provides evidence of the equivalence of primers in amplification. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function in amplification of a known target, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success in amplifying a known target.

Designing primers and probes which are equivalents to those taught in the art is routine experimentation. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, to design a number of primer and probe oligonucleotides to detect

enterovirus as taught by Lee and Verstrepen, including the instantly claimed oligonucleotides. The prior art, as exemplified by Hogan, teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested new primers and probes to obtain additional oligonucleotides that function to detect enterovirus and identify oligonucleotides with improved properties. The ordinary artisan would have a reasonable expectation of success of obtaining additional probes from within the sequence provided by Lee, as well as the regions specifically taught by Lee to target, including degenerate positions, as well as the oligonucleotides taught by Lee and Verstrepen. The instantly claimed sequences target regions of the enteroviral genome which the prior art of Lee and Verstrepen have already taught as targets, and in each case, represent sequences for which the prior art has already designed oligonucleotides with significant overlap. The prior art of Lee and Verstrepen teach a reasonable expectation of success that targeting such regions will successfully identify a broad range of different enteroviruses (see page 4094 of Verstrepen; Col. 14 - Table 3 of Lee).

Thus, for the reasons provided above, the ordinary artisan would have been motivated to design additional primers and probes, including the instantly claimed oligonucleotides, using the teachings in the art at the time the invention was made.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton
Primary Examiner
Art Unit 1634
4/21/06